The opinion in support of the decision being entered today
was not written for publication and is not precedent of the Board.

Paper No. 49

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte NORBERT HEIMBURGER, GERHARD KUMPE,
and KLAUSE WELLNER

_____

Appeal No. 1997-3501
Application No. 08/253,232

_____

ON BRIEF

_____

Before WINTERS, ROBINSON, MILLS Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 2-4, 6, 8-10, 16, 19, 21, 24-28 and 30, which are all of the claims pending in this application.

We reverse.

Claim 24 is illustrative of the claims on appeal and reads as follows:

24. A process for the preparation of a pasteurized and purified von Willebrand factor concentrate, which comprises:

a) preparing a solution selected from the group consisting of cryoprecipitate, Cohn fraction I, a supernatant of a cell culture and an extract of a cell culture, said solution having a pH of 5.5 to 7.3, and containing von Willebrand factor (vWF) as a complex with F VIII:C, a carbohydrate at a concentration of 5-30% w/w, calcium ion, and amino acids;

b) treating said solution with an anion exchanger to which F VIII:C binds to obtain a pasteurized von Willebrand factor concentrate free of F VIII:C;

c) treating said von Willebrand factor solution free of F VIII:C with 0.5 to 3 mol/l glycine to precipitate proteins from said solution;

d) removing said protein precipitate from said solution to form a glycine supernatant solution containing von Willebrand factor;

e) adding NaCl at a concentration of 2-15% w/v to said glycine supernatant solution to precipitate von Willebrand factor; and

f) recovering precipitated von Willebrand factor.

The prior art references relied upon by the examiner in rejecting the appealed claims are:

Kotitschke et al. (Kotitschke)	4,272,523	Jun. 9, 1981
Mitra et al. (Mitra)	4,543,210	Sep. 24, 1985
Mathews et al. (Mathews)	4,743,680	May 10, 1988
British Patent Application Costello	2 079 292	Jan. 20, 1980

Austen, "The Chromatographic Separation of Factor VIII on Aminohexyl Sepharose," British Journal of Haemophilia, Vol 43, pp. 669-74 (1979).

(Scopes), "Salting Out at High Salt Concentration," Protein Purification: Principles and Practice, Scopes, Ed., pp. 43-52 (1982).

Wang et al. (Wang), "Parenteral Formulation of Proteins and Peptides: Stability and Stabilizers," Journal of Parenteral Science and Technology, Vol 42, No. 25, pp. S3-S26 (1988).

(Harris), Protein purification methods: A practical approach, Harris, et al., Ed., IRL Press at Oxford University Press, New York, NY, pp. 57-64 (1989).

OPINION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, to the applied prior art, and to the respective positions articulated by the appellants and the examiner on the record before us. As a consequence of our review, we make the determinations which follow.

DECISION ON APPEAL

Claim Interpretation

Our appellate reviewing court stated in Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1567-1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), cert denied, 481 U.S. 1052 (1987):

> Analysis begins with a key legal question ! what is the invention claimed? Courts are required to view the claimed invention as a whole. 35 U.S.C. § 103. Claim interpretation, in light of the specification, claim language, other claims and prosecution history, is a matter of law and will normally control the remainder of the decisional process. [Footnote omitted.]

To that end, we note that during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). As background, Factor VIII is a complex of two components, Factor VIII:C and Factor VIII: vWF (also referred to as von Willebrand Factor), each with different genetic control and biochemical functions. Factor VIII:C serves as a coagulation promoting protein and Factor VIII: vWF serves as a platelet adhesion protein.[1] The invention of claim 24 is directed to a process for preparation of a pasteurized and purified von Willebrand factor (vWF) concentrate.

In claim 24, we interpret step "b) treating said solution with an anion exchanger to which F VIII:C binds to obtain a pasteurized von Willebrand factor concentrate free of F VIII:C;" consistent with the specification and prosecution history as meaning, "the factor VIII binds to basic ion exchangers . . . , whereas vWF remains in solution." Specification,

[1] See, e.g., U.S. Patent 4,822,472, filed May 15, 1987.

page 5, lines 26-32. Thus, vWF is not bound to the ion exchanger and is thus separated from FVIII:C which remains bound on the ion exchange column.

35 U.S.C. § 103

Claims 3, 6, 8-10, 16, 19, 24-25 and 30 stand rejected under 35 U.S.C. § 103 as obvious over Austen, in view of Mathews, Mitra, Wang, Costello, Scopes and Harris.

It is the examiner's position that (Answer, Paper No. 33, pages 6-7):

> [i]t would have been obvious to one with ordinary skill in the art at the time Applicants' invention was made to perform Austen's anion exchange procedure in the presence of Mathews' buffer components because these are stabilizing components that are of general usefulness in the purification of proteins, as additionally shown by Wang, and this would insure that the von Willebrand Factor would not become denatured during the purification procedure. It would also have been obvious to one with ordinary skill in the art at the time Applicants' invention was made to subject Austen's purified von Willebrand Factor to the precipitation protocols of Costello and Scopes because these are procedures that may be used and manipulated to (sic, so) that the desired protein is purified to the greatest extent possible, which, for a pharmaceutical preparation is desirable,, (sic) as the more highly purified a preparation is, the less likely there are to be contaminants present that would cause undesirable side effects. It would have been obvious to one with ordinary skill in the art at the time Applicants' invention was made to use NaCl as a precipitant in the purification procedure of Austen as modified by Costello, Mathews, and Scopes, because that is a salt that is known to be effective for the precipitation of proteins, as shown by Scopes. It would have been obvious to one with ordinary skill in the art at the time Applicant's invention was made to use Mitra's pasteurization procedure in the presence of Mitra's and Wang's protein stabilizers to inactivate viral or bacterial contaminants in the von Willebrand Factor preparation suggested by Austen as modified by Mathews, Costello and Scopes because it is desirable to have a pharmaceutical preparation that does not contain unwanted materials such as viruses, and heat treatment will inactivate these undesirable

> contaminants, and Mitra's and Wang's stabilizers will prevent denaturation of a protein during heat treatment procedures. It would have been obvious to one with ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal parameters of a protein purification procedure such as the buffer components and concentrations for all steps, and the type and concentration of precipitating agents and the types of purification steps as shown by Harris, because it is desirable to have a procedure that will enable the protein to be purified to the greatest extent with as few as contaminants as possible, and it is routine in the art to do so.

Austen describes the chromatographic separation of Factor VIII complexed with ristocetin, i.e., von Willebrand factor, on aminohexyl sepharose. After binding of the complex which includes the vWF, to aminohexyl sepharose, the ionic strength is gradually increased with sodium chloride, successively releasing ristocetin from Factor VIII, to allow purification of Factor VIII. Austen, page 672. The examiner acknowledges that Austen does not disclose components of the claimed chromatography buffers, does not teach precipitation steps in a process for the isolation of vWF, and does not teach pasteurization of vWF, or the conditions for pasteurization. Examiner's Answer, page 4.

The examiner relies upon Mathews for the disclosure that blood proteins, such as Factor VIII:C, may be purified by anion exchange chromatography in the presence of a sugar, sugar alcohol, amino acids and salt thereof, as well as the use of calcium chloride

as a buffer. Examiner's Answer, page 4. Mathews does not teach isolation, purification or pasteurization of vWF.

Costello is the only reference of record directly relating to the purification of vWF. Costello indicates that vWF may be produced by a process including steps of (i) treating a 3-4% PEG precipitate of a solubilized cryoprecipitate derived from blood with a solubilizer capable of taking up substantially all of the vWF present in the PEG precipitate, (ii) adding to the resulting solution of vWF a precipitant which is capable of preferentially precipitating fibrinogen with regard to the other components in the solution, (iii) treating the resulting supernatant with an adsorbent capable of adsorbing clotting factors II, VII, IX and X; (iv) treating the supernatant with a precipitant capable of precipitating substantially all of the protein present; and (v) solubilizing the precipitate with a solubilizer capable of taking up substantially all of vWF in the precipitate. Costello, page 1. Costello does not teach pasteurization of vWF or adsorbing only Factor VIII:C to an anion exchanger while maintaining vWF in solution.

Mitra discloses a process for producing a high purity antihemolitic factor VIII:C (AHF) concentrate which may be subjected to pasteurization. Mitra describes the pasteurization process as, "mixing AHF with at least one amino acid selected from glycine, lysine, arginine and alanine with at least about 30%, preferably from about 54% to saturation, on weight to volume basis of a compound selected from sugars and reduced

sugars such as sucrose and erythritol, respectively, to name representative examples. Then the mixture is heated at a temperature of about 60-75EC and at a pH of about 5.5-8.0 for at least about 10 hours." Mitra, column 7, lines 51-66. Mitra does not teach isolation, purification or pasteurization of vWF.

At page 47, Scopes indicates that the salting out of proteins follows the Hofmeister series, which includes Cl^-. Wang is relied on for the disclosure of generalized stabilization procedures for protein preparations with albumin, amino acids, and salts, including calcium ions. Examiner's Answer, page 5. Harris indicates that proteins have a unique set of properties which may be exploited in a purification protocol. Examiner's Answer, page 6.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). Rejection of claimed subject matter as obvious under 35 U.S.C. § 103 in view of a combination of prior art references requires consideration of whether the prior art, taken as a whole, would have suggested to those of ordinary skill in art that they should make the claimed composition or device, or carry out the claimed process, and whether prior art would, also, have revealed that such person would have had a reasonable expectation of success; both the suggestion and reasonable

expectation of success must be founded in prior art, not in applicants' disclosure. In re Vaeck, 947 F.3d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

As stated in Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629, (Fed. Cir. 1996) (citation omitted):

> It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references.

In the present case, the appellants argue that the examiner is merely picking and choosing from the cited references only those features that he finds can allegedly be used to render appellants' invention obvious under 35 U.S.C. § 103, and that this has been done without proper motivation. Brief, page 20.

In rebuttal, the examiner suggests that the reason, suggestion or motivation to modify or alter the procedure set forth in Austen for purifying Factor VIII, comes from the secondary references, in their general disclosure of the desirability to add steps to obtain higher purity, add stabilizers to retain activity and optimize conditions to streamline protocols. Paper No. 36, page 4.

While we would agree with the examiner that the prior art indicates a general desire to obtain compounds of higher purity and stability using streamlined protocols, the examiner has not established that the references, presently relied upon, would have

suggested or directed one of ordinary skill in the art to the presently claimed process or would have provided one of ordinary skill in the art with a reasonable expectation of success of doing so for vWF.

A general incentive does not make obvious a particular result, nor does the existence of isolated techniques by which that particular result can be obtained. See In re Deuel, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). What is lacking here is a suggestion, motivation or reason to be found, explicitly or implicitly, in the prior art for using the individual steps together in the claimed purification process to obtain purified vWF. In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1458 (Fed. Cir. 1998).

For example, the disclosures of Austen, Mathews, Wang and Mitra provide detailed procedures primarily for the purification of Factor VIII:C. They do not direct one of ordinary skill in the art to a process of purifying and isolating vWF.

The constituent factual findings for a prima facie case of obviousness are: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the prior art and the claimed invention. See Graham v. John Deere Co., 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

In the case before us, it is clear that the field and scope of the prior art, protein purification, remains unpredictable. As acknowledged by Harris at page 60, a universal purification strategy for all proteins cannot be given since the materials available and the requirements for each application differ. Harris, also, states that there is no substitute for trial and error. Wang recognizes that many variables affect protein stabilization and denaturation, including solvents, hydrophobic interactions, oxidation potential, temperature and pH, to name a few. Thus, the purification and pasteurization procedures for Factor VIII:C, provided in the cited references, would not necessarily provide one of ordinary skill in the art with the purification procedures for vWF, a different protein having different properties.

While Costello appears most relevant to the claimed method as it deals with purification of vWF, it does not address specifically the pasteurization conditions for vWF, and does not disclose the claimed purification process steps. The process of Costello starts with a precipitate of solubilized cryoprecipitate by product formed in the production of Factor VIII which includes vWF, and then solubilizes, precipitates, and resolubilizes vWF to effect purification. In contrast, the claimed method isolates vWF from solution only after having removed Factor VIII:C and other proteins and does not appear to require precipitation and resolubilization of vWF.

Furthermore, the examiner urges that there are no claim limitations directed to the binding abilities of the proteins being separated, and that this would support the relevancy of Austen to the claimed process. Paper No. 36, page 4. However, we interpret claim 1 as requiring only the binding of Factor VIII:C to the anion exchanger, while vWF remains in solution. Austen provides for the initial binding of Factor VIII complex (both Factor VIII:C and vWF) to aminohexyl sepharose, and does not suggest how one of ordinary skill in the art would alter this method to bind only Factor VIII:C while maintaining vWF in solution.

Thus, on this record, the examiner has failed to provide those facts or evidence which would establish a prima facie case of obviousness within the meaning of 35 U.S.C. § 103 as to the claimed subject matter. Where, as here, the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In view of the above, the rejection of claims 3, 6, 8-10, 16, 19, 24-25 and 30 is reversed.

35 U.S.C. § 103

Claims 2, 4, 21, and 26-28 stand rejected under 35 U.S.C. 103 as obvious over Austen, in view of Mathews, Mitra, Wang, Costello, Scopes, Harris as set forth above, in further view of Kotitschke.

Kotitschke describes the use of colloidal silica to separate fibrinogen from citrate plasma. The fibrinogen attaches to the colloidal silica while coagulation blood factors

remain preserved in the residual citrate plasma. Kotitschke, column 2, lines 33-39. In our view, Kotitschke does not overcome the above noted deficiencies of the combination of Austen, in view of Mathews, Mitra, Wang, Costello, Scopes, Harris. Therefore, the rejection of claims 2, 4, 21, and 26-28 under 35 U.S.C. 103 is reversed.

CONCLUSION

The rejections of the claims under 35 U.S.C. § 103 are reversed.

REVERSED

SHERMAN D. WINTERS Administrative Patent Judge	)
DOUGLAS W. ROBINSON Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
DEMETRA J. MILLS Administrative Patent Judge	)

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